EU Risk Management Plan

for

Trivalent Influenza Vaccine (Surface antigen, inactivated, adjuvanted, prepared in cell cultures)

RMP version to be assessed as part of this application:

RMP Version number:	1.0
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Summary of significant changes in this RMP:	Not applicable

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Abbreviations

Term / Abbreviation	Description
aTIVc	Trivalent Influenza Vaccine (surface antigen, inactivated, adjuvanted, prepared in cell cultures)
aQIVc	Quadrivalent Influenza Vaccine (surface antigen, inactivated, adjuvanted, prepared in cell cultures)
CT	Clinical Trial
DLP	Data Lock Point
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
HA	Haemagglutinin
IVE	Influenza Vaccine Effectiveness
NH	Northern Hemisphere
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
UK	United Kingdom
US	United States
WHO	World Health Organization

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Part I: Product(s) overview

Table Part I-1: Product(s) Overview

Active substance(s) (INN or common name)	Trivalent Influenza Vaccine (surface antigen, inactivated, adjuvanted, prepared in cell cultures; aTIVc)
Pharmacotherapeutic group(s) (ATC Code)	Influenza vaccine ATC Code: J07BB02
Name of Marketing Authorisation Applicant	Seqirus Netherlands B.V.
Medicinal products to which this RMP refers	One (aTIVc)
Invented name(s) in the European Economic Area (EEA)	Aujemflu
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	Chemical class: Influenza vaccine
	Summary of mode of action: aTIVc provides active immunisation against 3 influenza virus strains (2 A subtypes and 1 B type) by inducing humoral antibodies against haemagglutinin. These antibodies neutralise influenza viruses. This vaccine contains the adjuvant MF59C.1 (MF59), which is designed to increase and broaden the antigen-specific immune response and to extend the duration of the immune response.
	Important information about its composition: Influenza virus surface antigens (haemagglutinin and neuraminidase), inactivated, of the following strains*: aTIVc: A/H1N1, A/H3N2 and B/Victoria *Propagated in Madin Darby Canine Kidney cells Haemagglutinin per 1.0 ml dose: 45 micrograms per each influenza strain Adjuvant MF59C.1 containing per 1.0 ml dose: Squalene 19.5 milligrams Polysorbate 80 2.35 milligrams

	Sorbitan trioleate 2.35 milligrams Sodium citrate 1.32 milligrams Citric acid 0.08 milligrams It may contain traces of beta-propiolactone and cetyltrimethylammonium bromide which are used during the manufacturing process.
Hyperlink to the Product Information	aTIVc: SmPC
Indication(s) in the EEA	Current (if applicable): Prophylaxis of influenza in adults 50 years of age and older.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	Current (if applicable): One 1.0 mL dose.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	Current (if applicable): Suspension for injection in pre-filled syringe, 45 micrograms haemagglutinin per each influenza strain per 1.0 mL dose.
	Proposed (if applicable): Not applicable.
Will the product be subject to additional monitoring in the EU?	Yes

ATC = anatomic therapeutic chemical code; EEA = European Economic Area; EU = European Union; INN = International Nonproprietary Name; RMP = risk management plan

Part II: Safety Specification

Part II: Module SI - Epidemiology of the indication(s) and target population

Trivalent Influenza Vaccine (surface antigen, inactivated, adjuvanted, prepared in cell cultures; aTIVc) is indicated for prophylaxis of influenza in adults (50 years and older).

Influenza virus strains included in the aTIVc vaccine are the A/H1N1, A/H3N2 and B/Victoria strains.

Influenza Infection:

Influenza is an acute respiratory infectious disease of global importance caused by an influenza virus. In temperate climates, influenza generally affects people from November to March in the Northern Hemisphere (NH) and from May to September in the Southern Hemisphere. It can occur all year round in tropical climates (WHO, 2023). Influenza in humans can be caused by the influenza virus type A, B, and C, with the type A and type B viruses being the most clinically relevant.

Type A viruses are associated with annual epidemics and pandemics, and type B viruses contribute to the annual epidemics (WHO, 2023). The influenza type A virus can be further divided into subtypes based on the haemagglutinin (HA) and neuraminidase surface glycoprotein antigens. Of the influenza type A virus subtypes, the A/H3N2 and A/H1N1 subtypes are the most clinically important for annual influenza disease burden.

There are currently 2 known influenza B strains from 2 separate lineages, B/Yamagata and B/Victoria, that have circulated during previous influenza seasons. However, the B/Yamagata lineage circulation has not been confirmed since March 2020 (Paget et al, 2022). All influenza viruses experience some form of antigenic drift, but this is most pronounced in the influenza A virus for which new circulating variants are frequently observed over the influenza season. Such evolution of the influenza virus influences the host specificity and pathogenicity of these viruses, which can differ geographically, from season to season, and within a season.

Influenza Epidemiology:

Overall, the World Health Organization (WHO) estimates that worldwide annual influenza epidemics result in about one billion cases of seasonal influenza, including 3 to 5 million cases of severe illness, and about 290,000 to 650,000 deaths (WHO, 2023). In the

European Union (EU) / European Economic Area (EEA) region, seasonal influenza is estimated to cause up to 50 million symptomatic cases each year, and 15,000 to 70,000 European citizens die every year of causes associated with influenza (ECDC, 2022). In the United States (US), the Centers for Disease Control and Prevention estimates that influenza has resulted in between 9.4 to 45 million illnesses, between 100,000 to 710,000 hospitalisations and between 4,900 to 52,000 deaths annually between 2010 and 2022 (CDC, 2023a). Across age groups, the burden of influenza disproportionately falls on individuals < 5 years of age and ≥ 65 years of age (Neuzil et al, 2000; Rolfes et al, 2018; Thompson et al, 2009). There is also growing recognition of a high burden of influenza in adults 50-64 years of age (CDC, 2019).

The epidemiology of influenza in the population for whom aTIVc is indicated is described below.

Adults 50-64 Years Old - Epidemiology, Morbidity and Mortality

About one-fifth of the US population (approximately 63 million people) are aged between 50 and 64 years, and among these individuals, approximately one-third have an underlying medical condition that puts them at higher risk for influenza complications (CDC, 2019). In the US, the estimated rate of hospitalisations due to influenza disease is 3-fold higher in adults 50-64 years of age compared to the younger adult (18-49 years) age group (155.1 vs 48.4 per 100,000 population). Furthermore, the estimated number of medical visits due to influenza illnesses is higher in the 50-64 years age group (3.97 million) compared to older adults (1.72 million) (CDC, 2019).

The data from 10 influenza seasons between 1996-2006 in 5 European countries (Netherlands, United Kingdom [UK], France, Portugal, and Spain) show the percentage of all-cause mortality caused by influenza activity, in the age group 50-64 years old, ranged between 1.7-3.4% for the countries studied. The percentage of mortality due to respiratory disease caused by influenza activity was similar for the age groups 50-64 years (9.4-19.4%) and 65 years and older (9.4-19.3%). The percentage of mortality due to pneumonia and influenza caused by influenza activity was also similar for the age groups 50-64 years (11.8-24.5%) and 65 years and older (12.1-25.1%) (Nielen et al, 2010).

In the EU, seasonal influenza vaccine is recommended for older adults 50-64 years old (EU Vaccination Information Portal, 2022). In 2010, the Advisory Committee on Immunisation Practices acknowledged a high burden of influenza disease in individuals 50-64 years of age and, consequently, defined the risk group for older adults as 50 years and older. In the UK in

light of the risk of co-circulation of influenza and coronavirus disease 2019, the 2020 / 2021 national influenza vaccination program was extended to include adults 50-64 years of age for the 2020 / 2021, 2021 / 2022 and 2022 / 2023 influenza seasons (NHS, 2020; NHS, 2021; NHS, 2022). Vaccination has also been recommended for adults aged 50 years and older in Austria, for adults aged 55 years and older in Malta and Poland, and for adults aged 60 years and older in Germany, Greece, Hungary, Iceland, the Netherlands and Slovakia (ECDC 2022; Su et al, 2019).

Adults ≥ 65 Years – Epidemiology, Morbidity and Mortality

The higher burden of influenza among adults aged ≥ 65 years relative to younger adults is, in part, attributable to the age-related decline of the immune system (immunosenescence) (Lambert et al, 2012). Additionally, as individuals surpass 65 years, the prevalence of underlying medical conditions increases, as does frailty, and declines in functional status. This leads to heightened susceptibility to influenza infection and risk of serious complications, leading to increased influenza-related hospitalisations and deaths. Recognising their greater vulnerability, older adults are prioritised for vaccination (Grohskopf et al, 2022).

During most influenza seasons, individuals ≥ 65 years carry the heaviest burden of severe disease. Approximately 50-70% of hospitalisations due to influenza occur among this age group. In the UK, the influenza-related hospitalisation rate was estimated to be 101 per 100,000 for individuals 65 to 74 years of age, and 252 per 100,000 for individuals ≥ 75 years of age relative to the overall rate of 49 per 100,000 (Matias et al, 2016). In Norway from 2008 to 2017 the average hospitalisation rate in the age groups ranged from 62 per 100,000 for those who were 60 to 69 years of age to 241 per 100,000 in the 80+ year age group (Hauge et al, 2019). In Spain between NH 2010 / 2011 to NH 2015 / 2016, relative to those 15 to 65 years of age, cumulative rates for ≥ 65 years of age were approximately 3 times higher for severe hospitalised confirmed influenza cases, approximately 2 times higher for intensive care unit admissions, and approximately 6 times higher for deaths in influenza hospitalised patients (Oliva et al, 2018). In the US, the influenza-related hospitalisation rate over 15 seasons was estimated to be 309 per 100,000 in individuals ≥ 65 years of age versus a mean of 63.5 per 100,000 across all age groups (Zhou et al, 2012).

Influenza also contributes substantially to the mortality rate among ≥ 65 years of age. In the WHO EU region, of the more than 44,000 deaths occurring annually (ranging between approximately 28,000 to approximately 70,000 deaths per season) from influenza related

causes, approximately 75% of these deaths occur in individuals ≥ 65 years of age (Iuliano et al, 2018).

Demographics of the Population and Risk Factors for the Disease:

European Centre for Disease Prevention and Control (ECDC) and the WHO recommend annual seasonal influenza for specified risk groups (ECDC, 2023a; WHO, 2023). In the US, the Centers for Disease Control and Prevention recommends that everyone 6 months of age and older get a flu vaccine every year (CDC, 2023b) and notes flu vaccination is especially important for people at higher risk of influenza complications (CDC, 2023c).

Population groups at increased risk of influenza or complications due to influenza infection include:

- Older adults (ECDC), specifically (WHO) aged 65 years or older
- Younger Children (ECDC), specifically (WHO) children aged 6 through 59 months
- Individuals with chronic medical conditions such as chronic cardiac, pulmonary, renal, metabolic, neurodevelopmental, liver or haematologic diseases, and individuals with immunosuppressive conditions (such as human immunodeficiency virus / Acquired Immune Deficiency Syndrome), receiving chemotherapy or steroids, or malignancy
- Individuals with any condition compromising respiratory functions e.g., morbid obesity (body mass index > 40), and physical handicap in children and adults
- Pregnant women and women up to 2 weeks postpartum

The main existing treatment options:

Seasonal Influenza Vaccination

Vaccination is the most effective form of influenza prevention. The main objective of seasonal influenza vaccination is to reduce the risk for those who would be predisposed to complications if they were to become infected.

In 2003, the World Health Assembly, which includes all EU / EEA countries, recommended targeting 50% of the elderly for vaccination uptake by 2006 and 75% by 2010. Moreover, an EU target was set by the Council of all EU ministers of health of achieving 75% vaccination

coverage by 2014 to 2015 in the older age groups, and if possible, extending this to people with chronic conditions (ECDC, 2023b).

Personal Protective Measures

Public health management includes personal protective measures such as regular hand washing and proper drying of the hands or alcohol-based hand sanitisers; good respiratory hygiene and cough etiquette; self-isolation for those who feel unwell, feverish or have other symptoms of influenza; avoiding close contact with sick people and avoiding touching one's eyes, nose, or mouth; wearing face masks, particularly during the period when influenza and severe acute respiratory syndrome coronavirus 2 are co-circulating, especially for vulnerable categories, such as the elderly or those with underlying medical conditions (CDC, 2022; ECDC, 2022).

Symptomatic Treatment

Most simple seasonal influenza cases are managed symptomatically, and patients are advised to stay at home and rest to minimise the risk of infecting others in the community. Treatment focuses on reducing fever and relieving the symptoms. An influenza diagnosis can be confirmed by submitting nasopharyngeal specimens for laboratory analysis. It is considered important that patients monitor themselves to detect whether their condition deteriorates, and they require medical intervention (ECDC, 2022).

Antivirals

Antiviral treatment is recommended as soon as possible for any patient with suspected or confirmed influenza who is hospitalised; has severe, complicated, or progressive illness; or is at higher risk for influenza complications. Empiric antiviral treatment should be started as soon as possible in the above priority groups (CDC, 2023d).

There are 4 antiviral drugs approved by the European Medicines Agency (EMA) available in the EU Member States to treat influenza. These include oseltamivir, zanamivir, peramivir and baloxavir. For the best clinical benefit, treatment with antivirals should be given early in the infection, within 48 hours, (the earlier the better), to reduce the fever and flu-like symptoms (ECDC, 2022).

Part II: Module SII - Non-clinical part of the safety specification

aTIVc shares the same manufacturing platforms as quadrivalent influenza vaccine (surface antigen, inactivated, adjuvanted, prepared in cell cultures) (aQIVc) and only differs from aQIVc in the removal of the B/Yamagata strain. As such, the non-clinical data with aQIVc are applicable to aTIVc.

The nonclinical development of aTIVc is supported by immunogenicity data in CCI and a Good Laboratory Practice repeat-dose toxicity study in CCI .

Studies in CCI were performed using trivalent cell culture-derived antigens. The addition of MF59 resulted in increased haemagglutination inhibition titres and an increase in cytokine positive CD4+ T cells compared to nonadjuvanted antigens.

In Good Laboratory Practice Study No. CCI , male and female CCI received CCI doses of aQIVc, at CCI -week intervals. The clinical route of administration was used. All standard parameters for this type of study were evaluated, and immunogenicity was assessed using the haemagglutination inhibition assay. aQIVc was immunogenic and well-tolerated. In aQIVc-treated animals, findings at the injection sites with clinical pathology correlates and spleen effects, with full or partial recovery, were considered non-adverse and indicative of an immunogenic response to aQIVc administration. No evidence of local or systemic toxicity due to aQIVc was observed.

As per regulatory guidance (WHO, 2005), no secondary pharmacology, safety pharmacology, pharmacokinetic (absorption, distribution, metabolism, or excretion) or toxicokinetic studies were warranted. No single-dose, genotoxicity, or carcinogenicity studies have been conducted. Reproductive and developmental toxicity studies have not been performed with aTIVc due to sufficient nonclinical data available from studies conducted with each of the components of the vaccine, MF59 and TIVc.

Testing of MF59 Adjuvant

MF59 adjuvant was extensively evaluated in nonclinical studies. In repeat-dose rabbit studies, clinical pathology findings of increased fibrinogen and minor inflammatory; and degenerative changes at the injection site were consistent with the effects of intramuscular injections of an immunologically active material. These findings were reversible within days to 1 to 2 weeks and considered non-adverse.

MF59 did not affect cardiovascular and neurological parameters after repeated administrations in dogs. MF59 was not genotoxic (Ames test) or clastogenic (mouse micronucleus), was not a dermal sensitizer (Guinea pig), and was not teratogenic (rat and rabbit) or a developmental toxicant (rat).

Findings attributable to adjuvant were considered non-adverse with antigens combined with MF59 or MF59 alone. In general, although immunogenicity is enhanced, toxicology related findings with MF59-adjuvanted vaccines were comparable to findings with MF59 alone.

Conclusion on Nonclinical Data

In nonclinical studies, aTIVc or aQIVc were well tolerated and did not elicit local or systemic toxicity. There were no findings identified during nonclinical testing that warrant inclusion in the summary of safety concerns. No additional nonclinical studies were needed; the completed programme supports the proposed indication.

Part II: Module SIII - Clinical trial exposure

There are no ongoing or completed CSL Seqirus-sponsored investigational clinical trials (CTs) for aTIVc at the Data Lock Point (DLP) of this Risk Management Plan (RMP). aTIVc has not been used in any investigational CTs. aTIVc shares the same manufacturing platforms as aQIVc and only differs from aQIVc in the removal of the B/Yamagata strain. Therefore, it is assessed that the safety data from aQIVc studies are also applicable to aTIVc.

Since the Development International Birth Date of 29 September 2020, 4 CSL Seqirus-sponsored clinical studies have been conducted for aQIVc (V200_10, V201_01, V201_07 and V201_03), all of which were completed by the DLP of this RMP.

Overall, 10,037 subjects have been enrolled into the aQIVc clinical program, of which approximately 4,664 subjects have received standard dose or a high dose formulation of aQIVc (up to 45 µg - 3 times the standard dose - of HA antigen / strain [180 µg of HA antigen in total] and / or up to 29.25 mg - 3 times the standard dose- of MF59).

The overall cumulative subject exposure is provided in Table SIII-1, based upon treatment allocation for the 4 completed studies (V200_10, V201_01, V201_07 and V201_03).

Table SIII-1: Cumulative Subject Exposure to aQIVc in Clinical Trials

Vaccination / Number of Subjects	Completed Trials	Ongoing Trials	Total
aQIVc all dosages[a]	4664	N/A	**4664**
aQIVc (45,2)	3645	N/A	**3645**
aQIVc other dosages[b]	1019	N/A	**1019**
Influenza comparator (aQIV, QIVr, QIVc, QIVc(45,0)[c])	5373	N/A	**5373**
Total	**10,037**	N/A	**10,037**

Data from completed studies as of 26 February 2025.
aQIV = adjuvanted quadrivalent influenza vaccine; aQIVc = quadrivalent influenza vaccine (surface antigen, inactivated, adjuvanted, prepared in cell cultures); N/A = not applicable; QIVc = quadrivalent subunit inactivated cell-derived influenza vaccine; QIVr = nonadjuvanted quadrivalent recombinant influenza vaccine
[a] aQIVc formulations are described by their content in parentheses e.g., (45,2). The first number, 45, represents the antigen content (e.g., 45 µg HA per strain), and the second number represents the adjuvant content where 2 is 2x MF59 (i.e., 2 times the standard dose of MF59 in aQIV)
[b] aQIVc other dosages: ([15,1], [15,3], [30,2], [30,3], [45,1], [45,3]).
[c] QIVc (45,0) = nonadjuvanted quadrivalent cell-derived influenza vaccine containing 45 µg HA / strain.

The age and gender distributions of subjects treated with aQIVc and aQIVc (45,2) in completed CTs are summarised in Table SIII-2.

Table SIII-2: Age group and gender of subjects exposed to aQIVc and aQIVc (45,2)

	Number of Subjects Exposed to aQIVc (45,2)			Number of Subjects Exposed to aQIVc[a]		
Age group	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**
Adults (50 to 64 years)	797	1021	**1818**	1009	1339	**2348**
Elderly (65 to 75 years)	657	835	**1492**	840	1049	**1889**
Very Elderly (> 75 years)	154	181	**335**	202	225	**427**
Total	**1608**	**2037**	**3645**	**2051**	**2613**	**4664**

Data from completed studies as of 26 February 2025.
aQIVc = quadrivalent influenza vaccine (surface antigen, inactivated, adjuvanted, prepared in cell cultures)
[a] aQIVc all dosages: ([15,1], [15,3], [30,2], [30,3], [45,1], [45,2], [45,3]).

All subjects received a single dose of the vaccine.

Cumulative exposure to aQIVc and aQIVc (45,2) by ethnic origin from completed investigational trials are provided in Table SIII-3.

Table SIII-3: Ethnic origin of subjects exposed to aQIVc and aQIVc (45,2)

Ethnic Origin	**Number of Subjects Exposed to aQIVc (45,2)**	**Number of Subjects Exposed to aQIVc[a]**
American Indian or Alaska Native	6	10
Asian	655	768
Black or African American	205	362
White	2721	3376
Native Hawaiian or Other Pacific Islander	8	20
Other	50	128
Total	**3645**	**4664**

Data from completed studies as of 26 February 2025.
aQIVc = quadrivalent influenza vaccine (surface antigen, inactivated, adjuvanted, prepared in cell cultures)
[a] aQIVc all dosages: ([15,1], [15,3], [30,2], [30,3], [45,1], [45,2], [45,3])

Part II: Module SIV - Populations not studied in clinical trials

For aQIVc the populations not studied in CTs were those excluded according to eligibility criteria defined for the studies.

aQIVc studies did not include subjects < 50 years of age. This is also in line with the intended indication for aTIVc which is for adults of 50 years and older.

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

For aQIVc, the main exclusion criteria were:

- Due to the targeted age indication: females who are pregnant or lactating, absence of contraceptive methods for females of childbearing potential;
- Conditions that are likely to compromise the safety of the subject (e.g., hypersensitivity to any component of the vaccine, bleeding disorders, acute febrile illness, unstable clinical conditions, or history of demyelinating disease such as Guillain-Barré syndrome);
- Conditions that may interfere with the evaluation of vaccine-induced immune responses (such as other vaccinations, use of other investigational products, treatments that may impact systemic immune function or unstable abnormal function of the immune system).

Except for subjects with hypersensitivity to vaccine components, the other conditions are not considered contraindications to vaccination (see Table SIV.1-1 and Table SIV.1-2).

Table SIV.1-1: Important Exclusion Criterion, which will Remain as Contraindications, Warnings and Precautions

Criteria	Implications for Target Population
Hypersensitivity to the active substances, components of the adjuvant, excipients, residues	Persons with hypersensitivity must use alternative methods of prevention

Table SIV.1-2: Important Exclusion Criteria which are Not Proposed to Remain as Contraindications

Criteria	Reason for Exclusion	Justification for Not Being a Contraindication
Pregnant or lactating females, absence of contraceptive methods for females of childbearing potential	Targeted age indication Safety of subjects regarding investigational vaccine(s)	Due to the targeted age indication, aTIVc is not applicable to pregnant or breastfeeding women.
Bleeding disorder	Safety of subjects regarding investigational vaccine(s) Potential reactogenicity confounder	Benefit-risk is positive in this population with adequate warnings in the prescribing information.
History of Guillain-Barré syndrome (GBS) or other demyelinating disease such as encephalomyelitis and transverse myelitis	Safety of subjects regarding investigational vaccine(s) Potential safety confounder	Evidence for a causal relationship of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated.
Unstable abnormal function of the immune system	Potential immunogenicity confounder	Benefit-risk is positive in this population with adequate warnings in the prescribing information.
Progressive or unstable clinical conditions	Safety of subjects regarding investigational vaccine(s) Potential safety confounder	Benefit-risk is positive in this population with adequate warnings in the prescribing information.

aTIVc = trivalent influenza vaccine (surface antigen, inactivated, adjuvanted, prepared in cell cultures);
GBS = Guillain-Barré syndrome

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The aQIVc clinical development programmes are unlikely to detect certain types of adverse reactions such as very rare adverse reactions (1 in 10,000 people [< 0.01%]), adverse reactions with a long latency or those caused by prolonged or cumulative exposure (see Table SIV.2-1).

Table SIV.2-3: Limitations of Adverse Reaction Detection Common to Clinical Trial Development Programmes for aQIVc

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare	Approximately 4664[a] subjects were exposed to aQIVc in the clinical development program up to DLP of this RMP.	The number of subjects included in aQIVc studies (4664[a]) is sufficient to detect rare adverse reactions s, defined as with a frequency between 1:1000 to 1:10,000) if there were no background incidence (EMA / CHMP / VWP /457259 / 2014).
Due to prolonged exposure	Not applicable as this is a vaccine to be administered each influenza season.	Not applicable as this is a vaccine to be administered each influenza season.
Due to cumulative effects	Subjects were vaccinated only once with aQIVc.	Not applicable as this is a vaccine to be administered once each influenza season.
Which have a long latency	All phase 2 aQIVc studies had a 6-month safety follow-up. The Phase 3 clinical study had up to a 12-month safety follow-up.	Not applicable as vaccination (priming or seasonal revaccination) is conducted annually, so a period of 6 to 12 months safety follow-up is appropriate for this dosing frequency, for longer latency adverse reactions.

aQIVc = quadrivalent influenza vaccine (surface antigen, inactivated, adjuvanted, prepared in cell cultures); DLP = data lock point; RMP = risk management plan

[a] Figure from Table SIII-1

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3-1 outlines exposure estimates of populations under-represented in the pivotal CTs of aQIVc, and whether they are contraindicated populations.

Table SIV.3-1: Exposure of special populations included or not in clinical trial development programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme for aQIVc. Due to the targeted age indication, aTIVc is not applicable to these special populations.
Breastfeeding women	

Type of Special Population	Exposure
Subject with relevant comorbidities • Hepatic impairment • Renal impairment • Cardiovascular impairment	Not included in the clinical development programme for aQIVc due to potential safety confounder. - Patients with pulmonary, cardiovascular, renal, hepatic, neurologic, haematologic, metabolic impairment, or persons who are extremely obese are considered more at risk of complications from influenza and are therefore targeted for vaccination via public health campaigns or National Advisory Committee recommendations (Grohskopf et al, 2024). Although there are limited clinical data in these populations from the aQIVc clinical development programme: - Subjects with stable comorbidities were included in aQIVc phase 3 study V201_03. A post-hoc analysis of the immunogenicity of each vaccine performed by co-morbidity risk score in the V201_03 showed no correlation with immune response for aQIVc or any comparator. - In aQIVc studies V200_10 and V201_01, prior to study enrolment, demographic data was collected from the subjects, including age, sex, race, ethnicity, height and weight, prior influenza vaccination and comorbidity. Their risk of complications from influenza was calculated, incorporating medical comorbidity among other baseline characteristics, as per validated predictor of risk of complications from influenza in subjects ≥ 65 years of age (Hak et al, 2004). Using this model, a score of < 50 is considered low risk and a score of ≥ 50 high risk for hospitalisation due to pneumonia or influenza and death from any cause. - At postvaccination, similar proportions of subjects of high risk and low risk of influenza complications achieved haemagglutination inhibition (HI) titers ≥ 1:40. A trend to a lower seroconversion rate was seen in the high-risk group compared to the low-risk group. No clear pattern in Geometric Mean Titer ratios (GMTr) differences between high and low risk groups could be identified for aQIVc.
Subjects with unstable weakened immune function or receiving medications with potential impact on systemic immune function (such as chemotherapy, radiotherapy, chronic high dose corticosteroids or other immunomodulating agents)	Not included in the clinical development programme for aQIVc due to potential safety confounder. Though the immune response to aTIVc or aQIVc may be reduced in immunocompromised persons, including those receiving immunosuppressive therapy, this population is considered more at risk of complications from influenza and is therefore targeted for vaccination via public health campaigns and National Advisory Committee on Immunization Practices. Subjects with stable human immunodeficiency virus or other stable abnormal immune function were included in aQIVc phase 3 study V201_03.
Subjects with a target disease severity different from the inclusion criteria in the clinical trial population	Not applicable to aTIVc as the subjects included in CTs are given influenza vaccine prophylactically and represent the indicated population.

Type of Special Population	Exposure
Sub-populations carrying known and relevant polymorphisms	Not applicable to aTIVc
Children	The indication does not include children. Due to the age of the target population, these special populations are not applicable to aTIVc.
Elderly	The current indication of aTIVc is adults 50 years of age and older. Exposure estimates from clinical studies across all age groups are summarised in Table SIII-2. Half of the subjects in the aQIVc exposure dataset were adults aged 50-64 years (2,348), and the other half were elderly subjects: aged 65-75 years (1,889) and >75 years (427).
Population with relevant different ethnic origin	Not applicable to aTIVc. There were no restrictions on enrolment of subjects by racial and / or ethnic origin in aQIVc clinical development. Exposure estimates from clinical studies by subject race across all age groups are summarised in Table SIII-3. Most subjects in the aQIVc exposure dataset were of White, Asian or Black / African American race.

aQIVc = quadrivalent influenza vaccine (surface antigen, inactivated, adjuvanted, prepared in cell cultures);
aTIVc = trivalent influenza vaccine (surface antigen, inactivated, adjuvanted, prepared in cell cultures);
CT = clinical trial; HI = haemagglutination inhibition; GMTr = geometric mean titer ratio

Part II: Module SV – Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Not applicable

SV.1.2 Exposure

Not applicable

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable to influenza vaccines.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Since the aTIVc and aQIVc vaccines are both manufactured using the same process, and with overlapping compositions, it is considered that the data generated during the development of aQIVc to support its safety are relevant to aTIVc.

Based on the information from the aQIVc development program at the DLP of this RMP, there are no important identified risks, important potential risks, or missing information for aTIVc.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Local (injection or vaccination site) reactions including injection site erythema, injection site induration, injection site pain / tenderness, and injection site ecchymosis
- Generalised skin reactions including pruritus, urticarial and non-specific rash
- Systemic reactions including loss of appetite, nausea, vomiting, fatigue, myalgia, arthralgia, headache, chills, diarrhoea, and fever (≥ 38°C).

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Paraesthesia
- Extensive swelling of injected limb

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers:

- Anaphylaxis

Class effects for influenza vaccines:

- Bell's palsy
- Demyelination
- Encephalitis
- Guillain-Barré syndrome
- Haemolytic anaemia
- Immune thrombocytopenia
- Neuritis
- Vasculitis

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Based on the information from the aQIVc development program at the DLP of this RMP, there are no important identified or important potential risks for aTIVc.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Based on the information from the aQIVc development program at the DLP of this RMP, there are no important identified or important potential risks for aTIVc.

SVII.3.2 Presentation of the missing information

At the DLP of this RMP, there is no missing information for aTIVc.

Safety in immunocompromised individuals and safety in persons with underlying diseases is not considered as missing information on the basis that there is no evidence to suspect the possibility of a specific safety issue with use of influenza vaccine in immunocompromised patients and in populations with underlying diseases.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII-1: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risk	None
Important potential risk	None
Missing information	None

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for safety concerns:**

  None

- **Other forms of routine pharmacovigilance activities for adverse events following immunisation:**

  Periodic review of the following adverse events of special interest will be conducted using safety data received from post-marketing and Marketing Authorisation Holder-sponsored CT sources.
  - Autoimmune thyroiditis
  - Giant cell arthritis
  - Polymyalgia rheumatica

CCI [redacted]

- CCI [redacted]

III.2 Additional pharmacovigilance activities

Required additional pharmacovigilance activities

There is no additional pharmacovigilance activities required for aTIVc.

Additional pharmacovigilance activities recommended under EMA guidelines

In the Guideline on Influenza vaccines - Non-clinical and Clinical Module (EMA/CHMP/VWP/457259/2014), issued in July 2016, the EMA has recommended the

generation of brand-specific influenza vaccine effectiveness (IVE) data as a post-authorisation activity for seasonal influenza vaccines.

The implementation of IVE activities will be determined in alignment with EMA guidance current at the time of marketing authorisation, including any waivers, or alternative approaches agreed with the EMA, reflecting discussions on the feasibility and methodology of IVE data collection in the EU.

III.3 Summary table of additional pharmacovigilance activities

Table Part III.3-1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV: Plans for post-authorisation efficacy studies

Table Part IV-1: Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine risk minimisation measures

Table Part V.1-1: Description of routine risk minimisation measures by safety concern

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risks:	
None	Not applicable
Important Potential Risks:	
None	Not applicable
Missing Information	
None	Not applicable

V.2 Additional risk minimisation measures

Routine risk minimisation activities as described in Section V.1 are sufficient to manage the safety concerns for aTIVc. Additional risk minimisation measures are not necessary, as there are no important identified and potential risks or missing information to be addressed.

V.3 Summary of risk minimisation measures

Table Part V.3-2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks:		
None		
Important Potential Risks:		
None		
Missing Information		
None		

Part VI: Summary of the risk management plan

Summary of risk management plan for Trivalent Influenza Vaccine (surface antigen, inactivated, adjuvanted, prepared in cell cultures)

This is a summary of the risk management plan (RMP) for Trivalent Influenza Vaccine (surface antigen, inactivated, adjuvanted, prepared in cell cultures) (aTIVc). The RMP details important risks of aTIVc, how these risks can be minimised, and how more information will be obtained about aTIVc risks and uncertainties (missing information).

aTIVc Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how aTIVc should be used.

This summary of the RMP for aTIVc should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of aTIVc RMP.

I. The medicine and what it is used for

aTIVc is indicated for prophylaxis of influenza in adults 50 years and older (see SmPC for the full indication). It contains trivalent influenza vaccine (surface antigen, inactivated, adjuvanted, prepared in cell cultures) as the active substance and it is a suspension for injection in pre-filled syringe. It is to be administered as a single 1.0 mL dose by intramuscular injection.

Further information about the evaluation of aTIVc benefits can be found in aTIVc EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: link to the EPAR summary landing page.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of aTIVc, together with measures to minimise such risks and the proposed studies for learning more about aTIVc risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of aTIVc are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of aTIVc. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of medicine).

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks:		
None		
Important Potential Risks:		
None		
Missing Information		
None		

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of aTIVc.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for aTIVc.

Part VII: Annexes

Table of contents

CCI [redacted]

CCI [redacted]

CCI [redacted]

Annex 4 Specific adverse drug reaction follow-up forms

CCI [redacted]

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Annex 7 Other supporting data (including referenced material)

CCI [redacted]

Annex 4 Specific adverse drug reaction follow-up forms

Not applicable

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Not applicable

Annex 7 Other supporting data (including referenced material)

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